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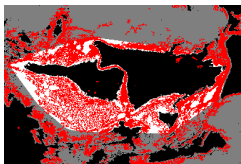
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April, 3rd 2017

To,
Professor F. Bonnet, *CHU de Rennes*,

Dear Editor-in-chief,

Please find enclosed the revised article entitled "Higher parathyroid hormone level is associated with increased below-knee artery calcification in type 2 diabetes" that we submitted for publication in *Diabetes & Metabolism*.

As you suggested, we accept to change the type of publication for a Research letter. By consequence, we have shortened the text to be in line with the recommendations.

I look forward to hearing from you at your earliest convenience,

Yours sincerely,
Dr Aurélien MARY

Prof Said Kamel

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Higher parathyroid hormone level is associated with increased below-knee artery calcification in type 2 diabetes.

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30 **Disclosure**

31 The authors have no conflicts of interest.

32

1 – Introduction

Vascular calcification (VC) is a pathological deposition of calcium-salts in the vasculature and constitutes an independent risk factor for cardiovascular disease (CVD) and mortality [1]. Type 2 diabetes is characterized by a high prevalence of tibial artery calcification [2], which in conjunction with atherosclerosis contributes to peripheral artery occlusive disease with foot ulcers and needs for leg amputation. A better understanding of the pathological mechanisms involved in below-knee VC is necessary to develop new therapeutic strategies aimed to avoid or to delay this dramatic complication of type 2 diabetes. Disorders of bone and mineral metabolism has been shown to confer an increased risk of VC per se [3,4] suggesting a link between impaired bone mineralization and excessive mineral deposition in the arterial wall. Of note, both high and low turnover forms of bone disease have been associated with VC. Since bone turnover is frequently decreased in type 2 diabetes [5], we postulated the possible existence of an association between below-knee VC and bone and mineral metabolism in patients with type 2 diabetes.

2 – Material and methods

We recently reported the set-up of a cross-sectional study entitled DIACART (for “Diabète et Calcification Artérielle”) [6]. A total of 198 patients were recruited during an 8-month period. Inclusion criteria were type 2 diabetes and at least one of the following parameters: (i) coronary artery disease, (ii) peripheral arterial occlusive disease, and (iii) age > 50 or > 60 years for men and women, respectively. Exclusion criteria were (i) an estimated glomerular filtration rate (eGFR) < 30 mL/min, as assessed by the modification of diet in renal disease equation, (ii) type 1 diabetes, and (iii) history of lower limb angioplasty or bypass. In these 198 patients, we measured the circulating levels of the bone resorption marker carboxy-terminal type I collagen cross-links (CTX-I), the bone formation marker bone alkaline

phosphatase (BAP) as well as the circulating level of mineral metabolism markers including total 25-hydroxy vitamin D [25(OH) vitD], intact parathyroid hormone (iPTH), fibroblast growth factor 23 (FGF-23) and α -klotho. Below-knee artery calcification scoring was calculated after imaging with a 128-slice multidetector CT scanner (Somatom Definition Flash, Siemens Healthcare, Forchheim, Germany) in tibial region. An overall calcification score expressed in Agatston Units (AU) was calculated by adding the calcification scores of the main below-knee arteries, i.e. distal popliteal, anterior tibial, posterior tibial, and peroneal arteries (6).

Data are expressed as mean \pm standard deviation (median) for quantitative variables, and as frequency for qualitative variables, as appropriate. To describe the study population, patients were divided according to tertile groups for below-knee artery calcification scores, and presence or absence of biochemical hyperparathyroidism, as determined by the usual threshold of a serum iPTH level \geq 65pg/mL. Comparisons between tertile groups of calcification were performed with ANOVA followed by Tukey post-test or with χ^2 test followed by χ^2 post-test with Bonferroni correction. Comparisons between patients with or without biochemical hyperparathyroidism were performed with χ^2 test for qualitative variables and Student's t test or Mann Whitney test for continuous variables. Univariate logistic regression analyses were used to assess the association between scores of below-knee calcification and demographic, biochemical and clinical variables. Multivariable logistic regression was performed by including parameters that were identified in univariate analyses with $p < 0.10$.

3 – Results

In the population studied, the proportion of men and women was 80% and 20% respectively, mean age 64.4 years and mean estimated of duration of type 2 diabetes 14.6 years. Previous

CVD was recorded in 70% of the patients, and 82% had a diagnosis of arterial hypertension. History or active tobacco use was found in 119 patients (60%). Mean eGFR of the population was 76 ± 20 mL/min. The tertile groups for below-knee artery calcification scores were respectively low calcification (≤ 166 UA), intermediate calcification (167-1614 UA), and high calcification score (>1614 UA). Those with higher below-knee artery calcification scores tended to be of male gender and older age, to have lower eGFR, and to have more frequently CVD and neuropathy. Among the biochemical markers of bone turnover and mineral metabolism, only serum iPTH concentrations were significantly different between the three subgroups: 60.8 ± 30.7 and 57.6 ± 29.8 pg/mL in second and third tertiles with intermediate and high calcification scores versus 45.5 ± 18 pg/mL in first tertile with low calcification score ($p = 0.003$). The mean 25(OH) vitD concentration for the whole population (13.8 ± 8.4 ng/mL) was in the range reflecting vitamin D moderate deficiency [25(OH) vitD between 10 and 20 ng/mL [7]], and the mean CTX-I concentration (0.140 ± 0.133 ng/mL) was close to the lower limit of normal values for the assay kit used. Mean FGF-23 (27.4 ± 29.2 RU/mL) and α -klotho (826 ± 260 pg/mL) were also in the range of the usual values for the respective assays. Univariate logistic regression analysis corroborated that among bone and mineral markers, only higher iPTH values were associated with calcification scores greater than 166 (Figure 1A). The other variables significantly associated with higher calcification scores were age, male gender, previous CVD, tobacco use, retinopathy, and lower eGFR. When these variables were included in a multivariable analysis, serum iPTH remained independently associated with below-knee artery calcification scores (OR per 10 pg/mL increment: 1.26; 95% CI 1.09 – 1.45; $p = 0.035$, Figure 1B). When we studied the characteristics of the population according to biochemical hyperparathyroidism, we showed that in patients with iPTH values ≥ 65 pg/mL, serum 25(OH) vitD was significantly lower as compared to those with iPTH < 65 pg/mL (10.2 ± 6.8 ng/mL *versus* 15.0 ± 8.6 ng/mL; $p < 0.001$). Interestingly,

vitamin D deficiency (defined by 25(OH) vitD levels ≤ 10 ng/mL) was more frequently observed in patients with biochemical hyperparathyroidism (62.5% versus 28.9%; $p = 0.023$).

4 – Discussion

In the present work, we found that in patients with type 2 diabetes and high cardiovascular risk but no severe CKD, serum iPTH was significantly and independently associated with below-knee arterial calcification score. None of the other studied biochemical markers of bone and mineral metabolism was associated with calcification. In the general population [8] as well as in type 2 diabetes [9], it has been demonstrated that high plasma iPTH levels are independently associated with higher cardiovascular mortality risk. Our finding demonstrating an association between PTH and VC, suggests that PTH may contribute to CVD in type 2 diabetes through the development of VC. The mechanisms whereby PTH could contribute to VC and CVD in patients with normal or moderately altered kidney function are not clearly known. Secretion of PTH from parathyroid gland is triggered by low serum calcium, which in turn raises serum calcium through its decrease in renal excretion and its release from bone. Thus, one possible mechanism for the contribution of PTH to VC is an increase in bone turnover leading to a high serum calcium x phosphate product. In our study, while the mean serum BAP concentration was similar to that observed in men and post-menopausal women in the general population, mean serum CTX-I values were about two-fold lower, in line with the notion that type 2 diabetes is a state of low bone turnover [5]. Although influenced by PTH status, bone resorption level is rather low and seems not to impact below-knee VC. A disturbance of the FGF-23/ α -klotho axis could be another factor affecting both VC and bone mineralization [10]. In the present study, FGF-23 and α -klotho concentrations were in the range given by the manufacturer of the assay kits used and didn't associate with VC. Serum iPTH has been associated with progression of vascular or valvular calcifications in secondary

hyperparathyroidism due to CKD [11], in elderly patients without severe CKD [12] and in mild primary hyperparathyroidism [13]. Finally, a very recent study demonstrated in type 1 diabetes an association of higher PTH levels with increased arterial stiffness, which is a consequence of VC [14]. Taken together, these results and ours seem to support the view that biochemical hyperparathyroidism might accelerate the progression of VC in type 2 diabetes. As expected, in our study there was a significant relationship between serum iPTH and 25(OH) vitD. More than 60% of our patients with biochemical hyperparathyroidism presented severe vitamin D deficiency whereas only 3% of the total population received vitamin D supplementation. This high prevalence of vitamin D deficiency in type 2 diabetes should be given careful consideration, all the more since 25(OH) vitD was also found to be associated with micro- and macrovascular complications [15]. As vitamin D supplementation can quickly restore serum 25(OH) vitD concentration and reduce PTH levels, vitamin D supplementation could represent a therapeutic option to delay VC induced by hyperparathyroidism.

The strengths of the present study are the assessment of a below-knee artery calcification score by high-sensitivity CT scan and the simultaneous measurement of numerous parameters of bone and mineral metabolism. The study would have been strengthened by the measurement of circulating biomarkers in a healthy control group.

6 – Conclusion

In conclusion, we found that among circulating markers of bone and mineral metabolism, only serum iPTH levels was independently associated with below-knee artery calcification score in patients with type 2 diabetes. Increased iPTH values were related to severe vitamin D deficiency. Whether the avoidance of mild hyperparathyroidism by vitamin D

supplementation can prevent or retard lower limb vascular calcification in type 2 diabetes patients remains to be assessed in prospective randomized trials.

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FIGURE LEGEND

Figure 1: Association of below-knee artery calcification score with markers of bone and mineral metabolism (n=198). A. Odds ratio [95%CI] for each marker of bone and mineral metabolism was analysed by univariate logistic regression. B. Odds ratio [95%CI] for each variable was analysed by multivariable logistic regression. Only variables significantly associated with VC in univariate analyses were included in the multivariable model. Abbreviations: iPTH: intact parathyroid hormone; FGF-23: fibroblast growth factor; 25(OH) vitD: 25-hydroxyvitamin D; CTX-I: carboxy-terminal type I collagen crosslinks; BAP: bone-specific alkaline phosphatase; CVD: cardiovascular disease; eGFR: glomerular filtration rate.

Figure 1
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